Remarks

Claims 1-4, 6, and 10-20 were pending in the above-mentioned application. Claims 1-4, 6 and 15-20 have been cancelled. New claim 23 has been added to more particularly point out and distinctly claim that which Applicants consider to be their invention. New claims 23-32 have also been added.

Upon entry of the above-made amendments and new claims, claims 10-14 and 23-32 will be pending in the current application. A copy of the claims marked up showing the amendments, as well as a clean copy of the claims are attached hereto.

The amended claims and the new claims are fully supported in the specification as originally filed. The amendments and the new claims do not add new subject matter in contravention of 35 U.S.C. §132. Applicants respectfully request that the amendments and the new claims be entered.

The following remarks, in conjunction with the above amendments and new claims, are believed to be fully responsive to the Official Action.

THE REJECTION UNDER 35 U.S.C § 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

In the application, claim 6 was rejected under 35 U.S.C 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In response, Applicants have cancelled originally filed claim 6.

THE REJECTION UNDER 35 U.S.C § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

In the application, claims 1-4, 6 and 10-20 are rejected under 35 U.S.C 112, second paragraph as being indefinite. In particular, the Examiner has objected to several terms in phrases recited in the above-identified claims. In response, Applicants submit that each of these rejections have been overcome and/or obviated, as discussed in detail below.

First, the Examiner has rejected claims 1 and 19 for being indefinite because of the phrase "preferably". In response, Applicants have canceled claim 1 and have replaced same with new independent claim 23, lacking the cited phrase. Additionally, the new dependent claim 24 covers the preferred embodiment. Furthermore, Applicants canceled originally filed claim 19.

Next, the Examiner rejected claim 6 for having insufficient antecedent basis for the limitation "said change between two paramagnetic states" in the claim. In response, Applicants cancelled originally filed claim 6.

Further, the Examiner contends the phrase "porphyrin-like" in claim 11 is indefinite. In response, Applicants deleted the cited phrase from the claim.

The Examiner has further rejected claim 11 because the phrase "chelates having a square planar symmetry" is indefinite. In response, Applicants submit this phrase is well established in the art (see enclosed search results of a simple internet search (Google/Glossary and Dictionary of Terms & Terminology in Chemistry)).

Next, the Examiner contends that the term "normal or abnormal biological processes" in claim 15 is indefinite. In response, Applicants cancelled claim 15.

Claims 17 and 20 were rejected by the Examiner because the recitation of "a redox agent" is indefinite. In response, Applicants cancelled claims 17 and 20.

For all the above reasons, Applicants respectfully submit that each of the Examiner's rejections under 35 U.S.C 112, second paragraph has been overcome and/or obviated. Applicants therefore respectfully request reconsideration and withdrawal of the rejections.

THE REJECTION UNDER 35 U.S.C § 102(b) SHOULD BE WITHDRAWN

Claims 1-4, 6, 10, 12-20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Garrity (US 5,958,373). This rejection is respectfully traversed.

The present invention is directed to a method of detecting regions with decreased vascular perfusion in a human or non-human animal subject. The method includes the step of administering an effective amount of a magnetic resonance imaging contrast agent including a physiologically tolerable Europium (II) compound having a first oxidation state. The Europium (II) compound is oxidized *in vivo* to a Europium (III) compound having a second oxidation state. The oxidation states differ in relaxivity by a factor of at least 5, such that contrast difference is enhanced in regions with decreased vascular perfusion in which conversion between said oxidation states occurs. The method also includes generating an image of said subject.

The relaxivity of the contrast agents used in the method of the present invention is a result of a change in pH and that a lower pH is the result of a decreased vascular perfusion. Thus, the contrast agents used in the method of the invention are able to detect regions of decreased vascular perfusion. Further, new claim 23 is based on the specification, page 5, l. 2-20 where Europium (II) compounds are described as a preferred embodiment of the invention.

Garrity discloses a method of generating a contrast enhanced image of a human or non-human animal subject comprising administering a MRI contrast agent thereto. Said contrast agents may comprise Europium. However, Garrity is completely silent about Europium (II) compounds (= Eu^{2+}) and these compounds are the only compounds claimed in the method in the application. Europium is a lanthanide and thus belonging to

the same group of metals as Gd and Dy (disclosed by Garrity, col. 11, l. 33-34). According to Garrity, these lanthanide metals are preferrably used as Gd^{3+} and Dy^{3+} (col. 11, l. 34). In the method of the application, only Eu^{2+} compounds are useful. Further, Garrity is completely silent about a method of detecting regions with decreased vascular perfusion which is based on the fact that Eu(II) compounds are oxidized in such regions to Eu(III) compounds and that relaxivity of said Eu(II) and Eu(III) compounds differ by a factor of at least 5, thus making such compounds especially useful to enhance contrast difference in MRI imaging of said regions. Thus, as the present invention claims subject matter that Garrity fails to disclose, Applicants respectfully submit that the present invention is patentably distinguishable thereover. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1-4, 6, 10, 12, 15--20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Platzek (US 5,277,895). This rejection is respectfully traversed.

Platzek discloses a method of generating a contrast enhanced image of a human or non-human animal subject comprising administering a MRI contrast agent thereto. Said contrast agents may comprise Europium. However, Platzek is completely silent about Europium (II) compounds (= Eu^{2+}) and these compounds are the only compounds claimed in the method in the application. Further, preferred central lanthanide ions of the complexes disclosed for the use in MR diagnosis are all trivalent lanthanide ions (see col. 4, l. 40-45, praseodymium, neodymium, samarium, ytterbium, gadolinium, terbium, dysprosium, holmium, erbium, all trivalent). Regarding example 8, col. 18, europium

oxide (Eu_2O_3) is used as the starting compound. Europium in europium oxide is trivalent, i.e, Eu^{3+} (see also enclosed documents about europium oxide). Thus, the complex according to Example 8 contains Eu^{3+} and such a compound is neither useful nor claimed in the method of the invention. Further, Platzek is completely silent about a method of detecting regions with decreased vascular perfusion which is based on the fact that Eu(II) compounds are oxidized in such regions to Eu(III) compounds and that relaxivity of said Eu(II) and Eu(III) compounds differ by a factor of at least 5, thus making such compounds especially useful to enhance contrast difference in MRI imaging of said regions. Therefore, as Platzek fails to disclose each and every element of the claimed invention, Applicants submit that the present invention is patentably distinct thereover. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1-4, 6, 11 and 13-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sessler (US 5,599,923). This rejection is respectfully traversed.

Sessler discloses a method of generating a contrast enhanced image of a human or non-human animal subject comprising administering a MRI contrast agent thereto. Said contrast agents may comprise Europium. However, Sessler is completely silent about Europium (II) compounds (= Eu^{2+}) and these compounds are the only compounds claimed in the method in the application. In contrary thereto, Sessler explicitly discloses Eu^{3+} chelates (see col. 1, l. 36, col. 4, l. 26). As already stated above, such compounds are neither useful nor claimed in the method of the invention. Further, Sessler is completely silent about a method of detecting regions with decreased vascular perfusion

which is based on the fact that Eu(II) compounds are oxidized in such regions to Eu(III) compounds and that relaxivity of said Eu(II) and Eu(III) compounds differ by a factor of at least 5, thus making such compounds especially useful to enhance contrast difference in MRI imaging of said regions. Thus, as Sessler fails to disclose each and every element of the claimed invention, Applicants respectfully submit that the present invention is patentably distinct therefrom. Reconsideration and withdrawal of the rejection are respectfully requested.

Thus, Applicants respectfully submit that as each of the cited references fail to disclose each and every element of the claimed invention, the present invention is patentably distinct thereover. Applicants submit that each of the Examiner's rejections under 135 U.S.C. § 102(b) made in the instant application has been overcome and/or obviated and respectfully request that the rejections be withdrawn.

THE REJECTION UNDER 35 U.S.C § 103(a) SHOULD BE WITHDRAWN

Claims 1-4, 6. 10 and 12-20 are rejected under 35 U.S.C § 103(a) as being unpatentable over Meade (WO 96/38184) in view of Hollister (US 5,801,228) in further view of Platzek (US 5,277,895). This rejection is respectfully traversed.

Meade discloses a method of generating a contrast-enhanced image of a human or non-human animal subject comprising administering a MRI contrast agent thereto. The method comprises administering metal chelates comprising DTPA, DOTA etc. as

chelating molecules. The instantly claimed method encompasses contrast agents comprising the chelating molecules. As the Examiner stated, Meade fails to disclose that the chelates contain europium (II) as a metal ion.

Hollister also fails to disclose europium (II). Moreover, preferred lanthanide ions according to Hollister are all trivalent lanthanide ions such as Gd^{3+} and Dy^{3+} (see col. 6, l. 15-18 and examples). As a result, Applicants respectfully submit that Hollister fails to overcome the deficiencies of Meade in order to render the present invention obvious.

Platzek further fails to disclose europium (II). Moreover, according to the examples europium (III) oxide is used thus resulting in europium (III) compounds which can not be used in the method of the instant application. Applicants respectfully submit that not only does Platzek fail to cure the deficiencies of the other cited references, but Platzek actually teaches away from the present invention.

Thus, the skilled artisan would not have been motivated by Hollister and Platzek to modify the methods and compositions disclosed by Meade in such a way as to arrive at the present invention. Hollister and Platzek completely fail to disclose, teach, or suggest the use of europium (II) metal ions for the production of europium compounds which are useful compounds in contrast agents for MR imaging in a method of detecting regions with decreased vascular perfusion.

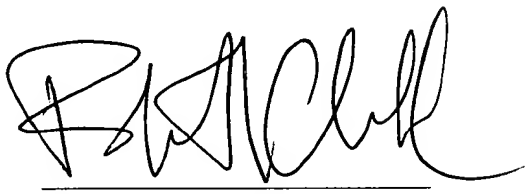
Furthermore, Applicants respectfully point out that neither Meade nor Hollister nor Platzek discloses a method of detecting regions with decreased vascular perfusion. Moreover, none of the references discloses that Eu(II) compounds could be used in such a method as they are oxidized in such regions to Eu(III) compounds and that relaxivity of said Eu(II) and Eu(III) compounds differ by a factor of at least 5, thus making such compounds especially useful to enhance contrast difference in MRI imaging of said regions.

As neither Meade, nor Hollister, nor Platzek, either singly or in combination disclose, teach, or suggest the method of the present invention, Applicants respectfully submit that the present invention is patentably distinguishable therover. Reconsideration and withdrawal of the rejection made under 35 U.S.C. § 103(a) are resepctfully requested.

In view of the amendments and remarks herein, Applicants believe that each ground for rejection or objection made in the instant application has been successfully overcome or obviated, and that all the pending claims, including claims 10-14 and 23-32, are in condition for allowance. Favorable action thereon is respectfully requested.

Any questions with respect to the foregoing may be directed to Applicants' undersigned counsel at the telephone number below.

Respectfully submitted,



Robert F. Chisholm
Registration No.: 39,939
Attorney for Applicants

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on 28 Jan 03

Melissa Leck
Signature
Date January 28, 2003

Amersham Biosciences Corp
800 Centennial Avenue
P. O. Box 1327
Piscataway, New Jersey 08855-1327

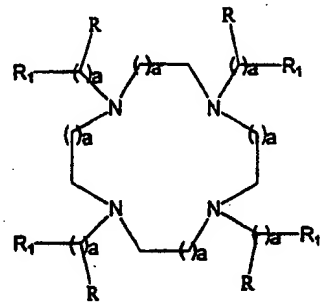
Tel: (609) 514-6905
Fax: (609) 514-6635

Claims (marked version showing amendments)

10. (twice amended) The method as claimed in claim [1]24, wherein said chelate complex is a complex of a chelant selected from the group consisting of DTPA, EDTA, DTPA-BMA, DO3A, DOTA, HP-DO3A, TMT and DPDP.

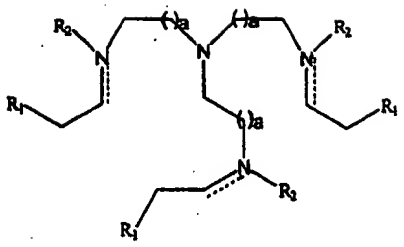
11. (twice amended) The method as claimed in claim [1]24, wherein said chelate complex is a complex of a chelant selected from the group consisting of porphyrins[and porphyrin-like molecules], phthalocyanins, crown ethers, hemin, heme, chelants having a square planar symmetry, cryptands and cryptates.

12. (twice amended) A method as claimed in claim [1]24, wherein said chelate complex is a complex of a chelant selected from compounds of formulae (I), (II), (III), (IV), (V) and (VI):



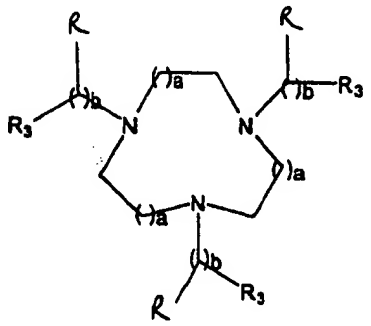
(I)

where each a independently represents an integer between 1 and 3, each R independently represents hydrogen or hydroxy and each R_1 independently represents a carboxylate, phosphate, thioacid, thiol, amino alkoxide or hydroxy group;



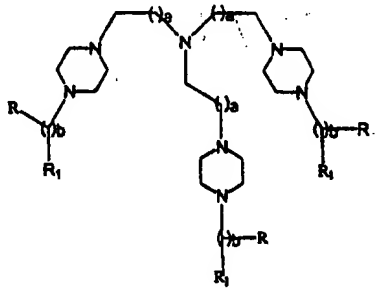
(II)

where a and R_1 are as hereinbefore defined and each R_2 independently represents hydrogen, C_{1-6} alkyl or aryl, with the proviso that R_2 is absent when the double bond is present on the same nitrogen;



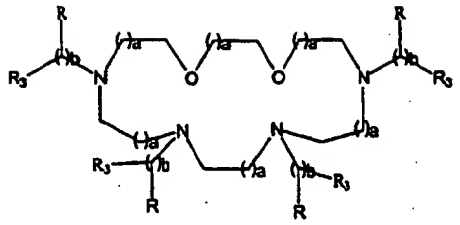
(III)

where a, R and R_2 are as hereinbefore defined, b is an integer between 0-3 and each R_3 independently represents R_1, $NR\text{-}NR_2\text{-}COO^{\theta}$, or $N{=}N\text{-}COO^{\theta}$ when b is positive or each R_3 independently represents $N{=}CH\text{-}COO^{\theta}$ or $NR_2\text{-}CH_2\text{-}COO^{\theta}$;



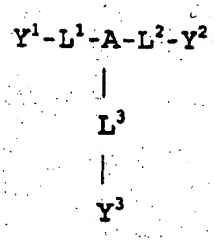
(IV)

where a, b, R and R_1 are as hereinbefore defined;



(V)

where a, b, R and R_3 are as hereinbefore defined;



(VI)

where A is N, CR_4, P, P=O, *cis,cis,cis*-1,3,5-trisubstituted-cyclohexane or an N,N',N"-triosubstituted-triaza 9 to 14 membered macrocyclic ring;

L^1,L^2,L^3 are linker groups which are independently chosen from C_{1-4} alkylene, C_{4-8} cycloalkylene or C_{4-8} o-arylene;

Y^1,Y^2,Y^3 are independently chosen from $-NH_2$, -B(=O)OZ, $-N=CR_5$-B(=O)OZ, $-NR_5$-CR_6-(=O)OZ, $-N[CR_6-B(=O)Q]_2$ and $-O-CR_6$-B(=O)OZ where B is C or PR_6, each Q is independently –OZ or $-NR_6$, and Z is H or a counter-ion;

each R_4 and R_5 group is independently chosen from H, C_{1-5} alkyl, C_{1-5} alkoxyalkyl, C_{1-5} hydroxyalkyl, C_{1-5} aminoalkyl, C_{5-10} aryl or C_{1-6} fluoroalkyl;

R_6 is OH, C_{1-6} alkyl, C_{1-6} alkoxyalkyl, C_{1-6} fluoroalkyl, C_{1-10} alkoxy or C_{5-10} aryl;

with the proviso that at least one of Y^1, Y^2 and Y^3 is $-N=CR_5$-B(=O)OZ.

13. (twice amended) The method as claimed in claim [1]23, wherein said contrast agent is conjugated to a biological vector capable of targeting said contrast agent to a desired region of the body.

14. (once amended) The method as claimed in claim 13, wherein said biological vector is selected from the group consisting of an antibody, [and]an antibody fragment, and an oligonucleotide binding motif.